



Clinical trial results:

Randomized, Double-Blind, Phase 3 Trial to Compare the Efficacy of Ipilimumab vs Placebo in Asymptomatic or Minimally Symptomatic Patients with Metastatic Chemotherapy-Naïve Castration Resistant Prostate Cancer

Summary

EudraCT number	2009-016217-23
Trial protocol	NL ES GB DE SE CZ DK HU IT GR
Global end of trial date	17 July 2015

Results information

Result version number	v1 (current)
This version publication date	30 July 2016
First version publication date	30 July 2016

Trial information

Trial identification

Sponsor protocol code	CA184-095
-----------------------	-----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01057810
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Bristol-Myers Squibb International Corporation, Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, clinical.trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, clinical.trials@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to compare overall survival of subjects with chemotherapy-naïve castration resistant prostate cancer (CRPC) who were randomised to ipilimumab vs placebo.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 July 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 269
Country: Number of subjects enrolled	Argentina: 34
Country: Number of subjects enrolled	Brazil: 42
Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Chile: 36
Country: Number of subjects enrolled	Colombia: 19
Country: Number of subjects enrolled	Czech Republic: 18
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	France: 45
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 25
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Mexico: 33
Country: Number of subjects enrolled	Netherlands: 41
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Spain: 48
Country: Number of subjects enrolled	Sweden: 12

Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Austria: 65
Worldwide total number of subjects	837
EEA total number of subjects	371

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	217
From 65 to 84 years	602
85 years and over	18

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

837 subjects enrolled; 602 randomized; 598 treated. Of the 235 not randomized, 189 no longer met criteria, 28 withdrew consent, 2 suffered Adverse Events, 2 were non-compliant, 1 was lost to follow-up, and 13 were removed for other/unspecified reasons. Post-randomization, 4 no longer met criteria and were not treated (3 placebo, 1 ipilimumab).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects were administered with ipilimumab matching placebo infusion (normal saline or 5% dextrose) at a dose of 2 milliliter/kilogram (mL/kg) intravenously (IV) over 90 minutes. Induction dosing occurred on Days 1, 22, 43, and 64 during the Induction phase and every 12 weeks starting at Week 24 during the Maintenance phase until unacceptable toxicity, clinical deterioration, confirmed disease progression, or study closure.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered with placebo 2 mg/kg IV over 90 minutes.

Arm title	Ipilimumab
------------------	------------

Arm description:

Subjects were administered with ipilimumab 10 mg/kg IV over 90 minutes with a normal saline flush at the end. Induction dosing occurred on Days 1, 22, 43, and 64 during the Induction phase and every 12 weeks starting at Week 24 during the Maintenance phase until unacceptable toxicity, clinical deterioration, confirmed disease progression, or study closure.

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered with ipilimumab 10 mg/kg IV over 90 minutes.

Number of subjects in period 1^[1]	Placebo	Ipilimumab
Started	202	400
Completed	1	1
Not completed	201	399
Adverse event, serious fatal	2	12
Consent withdrawn by subject	10	25
No longer met study criteria	-	1
Disease progression	156	197
Study drug toxicity	5	114
Maximum clinical benefit	5	5
Adverse event unrelated to study drug	13	29
Randomised but not treated	3	1
Unspecified	7	14
Poor/non-compliance	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of 837 subjects who were enrolled, 602 subjects were randomised. Reasons: 189 subjects no longer met criteria, 28 subjects withdrew consent, 2 subjects suffered Adverse Events, 2 subjects were non-compliant, 1 subject was lost to follow-up, and 13 subjects were removed for other/unspecified reasons.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects were administered with ipilimumab matching placebo infusion (normal saline or 5% dextrose) at a dose of 2 milliliter/kilogram (mL/kg) intravenously (IV) over 90 minutes. Induction dosing occurred on Days 1, 22, 43, and 64 during the Induction phase and every 12 weeks starting at Week 24 during the Maintenance phase until unacceptable toxicity, clinical deterioration, confirmed disease progression, or study closure.	
Reporting group title	Ipilimumab
Reporting group description:	
Subjects were administered with ipilimumab 10 mg/kg IV over 90 minutes with a normal saline flush at the end. Induction dosing occurred on Days 1, 22, 43, and 64 during the Induction phase and every 12 weeks starting at Week 24 during the Maintenance phase until unacceptable toxicity, clinical deterioration, confirmed disease progression, or study closure.	

Reporting group values	Placebo	Ipilimumab	Total
Number of subjects	202	400	602
Age, Customized Units: subjects			
< 65 years	65	104	169
>= 65 years	137	296	433
Age Continuous Units: years arithmetic mean full range (min-max)	68.6 42 to 92	69.3 44 to 91	-
Gender, Male/Female Units: subjects			
Female	0	0	0
Male	202	400	602
Region of Enrollment Units: Subjects			
North America	79	154	233
South America	25	52	77
Europe	74	161	235
Australia	24	33	57

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects were administered with ipilimumab matching placebo infusion (normal saline or 5% dextrose) at a dose of 2 milliliter/kilogram (mL/kg) intravenously (IV) over 90 minutes. Induction dosing occurred on Days 1, 22, 43, and 64 during the Induction phase and every 12 weeks starting at Week 24 during the Maintenance phase until unacceptable toxicity, clinical deterioration, confirmed disease progression, or study closure.	
Reporting group title	Ipilimumab
Reporting group description:	
Subjects were administered with ipilimumab 10 mg/kg IV over 90 minutes with a normal saline flush at the end. Induction dosing occurred on Days 1, 22, 43, and 64 during the Induction phase and every 12 weeks starting at Week 24 during the Maintenance phase until unacceptable toxicity, clinical deterioration, confirmed disease progression, or study closure.	

Primary: Overall Survival (OS) Time

End point title	Overall Survival (OS) Time
End point description:	
OS was defined as the time from the date of randomisation until the date of death. For subjects without documentation of death, OS was censored at the last date the subject was known to be alive. The analysis was performed in all randomized subjects defined as all subjects who were randomized to a treatment arm.	
End point type	Primary
End point timeframe:	
Randomisation up to 57 months	

End point values	Placebo	Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	400		
Units: months				
median (confidence interval 95%)	29.73 (26.12 to 34.17)	28.65 (24.48 to 32.46)		

Statistical analyses

Statistical analysis title	Overall Survival Time of Ipilimumab
Statistical analysis description:	
Treatment comparison was estimated by Kaplan-Meier estimation for the overall survival time based on treatment (Placebo and Ipilimumab).	
Comparison groups	Ipilimumab v Placebo

Number of subjects included in analysis	602
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3667
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95.87 %
sides	2-sided
lower limit	0.88
upper limit	1.39

Secondary: Progression-Free Survival (PFS) Time

End point title	Progression-Free Survival (PFS) Time
End point description:	
Progression-free survival, as determined by the investigator, was defined as the time from randomisation to the earliest date of confirmed Prostate-Specific Antigen (PSA) progression, confirmed radiological progression, clinical deterioration, or death. The analysis was performed in all randomized subjects defined as all subjects who were randomized to a treatment arm.	
End point type	Secondary
End point timeframe:	
Randomisation up to 57 months	

End point values	Placebo	Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	400		
Units: months				
median (confidence interval 95%)	3.81 (2.76 to 4.11)	5.59 (5.32 to 6.28)		

Statistical analyses

Statistical analysis title	Progression-Free Survival Time of Ipilimumab
Statistical analysis description:	
Treatment comparison was estimated by Kaplan-Meier estimation for the overall survival time based on treatment (Placebo and Ipilimumab).	
Comparison groups	Placebo v Ipilimumab
Number of subjects included in analysis	602
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.8

Secondary: Time to subsequent non-hormonal cytotoxic therapy

End point title	Time to subsequent non-hormonal cytotoxic therapy
-----------------	---

End point description:

For subjects who discontinued treatment or experienced disease progression while on study therapy and then received subsequent non-hormonal cytotoxic therapy, time to subsequent non-hormonal cytotoxic therapy was defined as the time from randomisation to the time of initiation of subsequent non-hormonal cytotoxic therapy. Subjects who did not receive subsequent non-hormonal cytotoxic therapy were censored on the last known alive date (for subjects who have not died) or the date of last follow-up contact at which the subjects was known alive (for subjects who died). The analysis was performed in all randomized subjects defined as all subjects who were randomized to a treatment arm.

End point type	Secondary
----------------	-----------

End point timeframe:

Randomisation up to 57 months

End point values	Placebo	Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	199		
Units: months				
median (confidence interval 95%)	10.91 (8.44 to 14.59)	18.04 (15.18 to 24.8)		

Statistical analyses

Statistical analysis title	Time to subsequent cytotoxic therapy of Ipilimumab
Comparison groups	Placebo v Ipilimumab
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95.87 %
sides	2-sided
lower limit	0.52
upper limit	0.83

Secondary: Time to Pain Progression

End point title	Time to Pain Progression
End point description:	
Time to pain progression was defined as time from randomisation to the time of the earliest date of any of the following 4 events: 1) an increase in average daily worst pain intensity of ≥ 2 points from baseline according to the Brief Pain Inventory - Short Form (BPI-SF), maintained over 2 consecutive time periods. 2) initiation of opioid analgesic (excluding codeine or dextropropoxyphene). 3) initiation of palliative radiotherapy for prostate cancer. 4) increase in mean Analgesic Score (AS) of $\geq 25\%$ from baseline (for subjects with baseline AS > 10) or increase in mean AS ≥ 10 points from baseline (for subjects with baseline AS ≤ 10). Subjects who did not experience any of these events were censored on the earliest date among the latest BPI-SF completion date with non-missing worst pain assessment and last evaluable disease assessment date as defined in the PFS censoring mechanism. The analysis was performed in all randomized subjects. Here, '99999' represents not estimable data.	
End point type	Secondary
End point timeframe:	
Randomisation up to 57 months	

End point values	Placebo	Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	400		
Units: months				
median (confidence interval 95%)	16.62 (11.53 to 99999)	21.68 (19.22 to 99999)		

Statistical analyses

Statistical analysis title	Time to Pain Progression of Ipilimumab
Comparison groups	Placebo v Ipilimumab
Number of subjects included in analysis	602
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95.87 %
sides	2-sided
lower limit	0.71
upper limit	1.35

Secondary: Number of subjects who died or had Adverse Events (AEs), Serious Adverse Events (SAEs), immune-related AEs (irAEs), or immune-mediated adverse reactions (imARs), Drug related AEs and Grade 3-4 AEs

End point title	Number of subjects who died or had Adverse Events (AEs), Serious Adverse Events (SAEs), immune-related AEs (irAEs), or immune-mediated adverse reactions (imARs), Drug related AEs and Grade 3-4 AEs
-----------------	--

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death,

persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalisation. irAE=AEs consistent with an immune mediated mechanism. imAR=AEs of special interest that were adjudicated as imAR by investigator. Treatment-related=having certain, probable, possible, or missing relationship to study drug. Grade (Gr) 1=Mild, Gr 2=Moderate, Gr 3=Severe, Gr 4= Potentially Life-threatening or disabling. Events were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The analysis was performed in treated subjects defined as all subjects who received at least 1 dose of ipilimumab or placebo.

End point type	Secondary
End point timeframe:	
Day 1 of study therapy to last dose plus 70 days	

End point values	Placebo	Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	399		
Units: subjects				
number (not applicable)				
AEs (grade 3-4) (n=0,1)	59	223		
Drug-related AE (any grade)	98	325		
Drug-related AE (grade 3-4)	11	158		
SAEs (any grade)	53	213		
SAEs (grade 3-4)	39	153		
AE leading to DC (any grade)	20	139		
AE leading to DC (grade 3-4)	14	103		
irAEs (any grade)	57	309		
irAE (grade 3-4)	3	125		
imAR (grade ≥ 2)	14	273		
Deaths	130	259		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treated subjects with Grade 3 or 4 clinical laboratory abnormalities

End point title	Number of treated subjects with Grade 3 or 4 clinical laboratory abnormalities
-----------------	--

End point description:

NCI CTC, Version 3 used to assess parameters. LLN=lower limit of normal. ULN=upper limit of normal. CTC criteria: White blood cells (WBC): Gr 3: <2.0 to 1.0*10⁹/L, Gr 4: <1.0*10⁹/L. Absolute neutrophil count (ANC): Gr 3: <1.0 to 0.5*10⁹/L, Gr 4: <0.5*10⁹/L. Platelet count: Gr 3: <50.0 to 25.0*10⁹/L, Gr 4: <25.0 to 10⁹/L. Hemoglobin: Gr 3: <8.0 to 6.5 g/dL, Gr 4: <6.5 g/dL. Absolute Lymphocyte Count (ALC): Gr 3: 0.2 - <0.5*10⁹/L, Gr 4: <0.2*10⁹/L. Lipase: Gr 3: >2.0 - 5.0*ULN; Gr 4: >5.0*ULN. Amylase: Gr 3: >2.0 - 5.0*ULN; Gr 4: >5.0*ULN. Alanine aminotransferase (ALT) Gr 3: >5.0 - 20.0*ULN; Gr 4: >20.0*ULN. Aspartate Aminotransferase (AST): Gr 3: >5.0 - 20.0*ULN; Gr 4: >20.0*ULN. Bilirubin: Gr 3: >3.0 - 10.0*ULN; Gr 4: >10.0*ULN. Alkaline Phosphatase: Gr 3: >5.0 - 20.0*ULN; Gr 4: >20.0*ULN. Creatinine: Gr 3: >3.0-6.0*ULN, Gr 4: >6.0*ULN. The analysis was performed in treated subjects defined as all subjects who received at least 1 dose of ipilimumab or placebo.

End point type	Secondary
----------------	-----------

End point timeframe:

Randomisation up to 57 months

End point values	Placebo	Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	399		
Units: subjects				
number (not applicable)				
WBC (n=195;383)	0	3		
ANC (n=195;383)	0	2		
Platelet count (n=194;381)	0	2		
Hemoglobin (n=195;383)	2	5		
ALC (n=195;383)	4	12		
Lipase (n=196;382)	4	27		
Amylase (n=198;385)	2	9		
ALT (n=198;386)	1	16		
AST (n=196;383)	1	18		
Total Bilirubin (n=198;386)	0	4		
Alkaline phosphatase (n=196;383)	11	18		
Creatinine (n=9;23)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-Study (Day 1 of study therapy to last dose plus 70 days).

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	17.1
--------------------	------

Reporting groups

Reporting group title	Ipilimumab
-----------------------	------------

Reporting group description:

Subjects were administered with ipilimumab 10 mg/kg IV over 90 minutes with a normal saline flush at the end. Induction dosing occurred on Days 1, 22, 43, and 64 during the Induction phase and every 12 weeks starting at Week 24 during the Maintenance phase until unacceptable toxicity, clinical deterioration, confirmed disease progression, or study closure.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Subjects were administered with ipilimumab matching placebo infusion (normal saline or 5% dextrose) at a dose of 2 milliliter/kilogram (mL/kg) intravenously (IV) over 90 minutes. Induction dosing occurred on Days 1, 22, 43, and 64 during the Induction phase and every 12 weeks starting at Week 24 during the Maintenance phase until unacceptable toxicity, clinical deterioration, confirmed disease progression, or study closure.

Serious adverse events	Ipilimumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	213 / 399 (53.38%)	53 / 199 (26.63%)	
number of deaths (all causes)	35	5	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			

subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	12 / 399 (3.01%)	8 / 199 (4.02%)	
occurrences causally related to treatment / all	0 / 12	0 / 9	
deaths causally related to treatment / all	0 / 12	0 / 4	
Metastases to central nervous system			
subjects affected / exposed	1 / 399 (0.25%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			
subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal cancer			
subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			

subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 399 (0.75%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic infarction			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	4 / 399 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 399 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 399 (0.50%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 399 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Fatigue			
subjects affected / exposed	11 / 399 (2.76%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	7 / 12	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrosis			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	3 / 399 (0.75%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-Organ failure			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	3 / 399 (0.75%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	0 / 399 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	14 / 399 (3.51%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	8 / 16	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sudden death			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			

subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	7 / 399 (1.75%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	3 / 8	0 / 0	
deaths causally related to treatment / all	2 / 3	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	2 / 399 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	6 / 399 (1.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 399 (0.25%)	4 / 199 (2.01%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed mood			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug dependence			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-Induced psychotic disorder			

subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 399 (1.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 399 (1.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	2 / 399 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Weight decreased subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Overdose			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord injury			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	8 / 399 (2.01%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 11	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	3 / 399 (0.75%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	2 / 3	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 399 (0.75%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory arrest			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery insufficiency			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 399 (0.75%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral thrombosis			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cluster headache			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve disorder			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			

subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ivth nerve paresis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mononeuropathy			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor dysfunction			

subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis crisis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 399 (0.25%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	5 / 399 (1.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viith nerve paralysis			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			

subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bandaemia			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow disorder			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 399 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell disorder			

subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorder			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	5 / 399 (1.25%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	3 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coeliac disease			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	27 / 399 (6.77%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	29 / 32	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	47 / 399 (11.78%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	54 / 59	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 399 (0.75%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	3 / 399 (0.75%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			

subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Megacolon			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	10 / 399 (2.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	7 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	6 / 399 (1.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	3 / 399 (0.75%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	3 / 399 (0.75%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminaemia			

subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	4 / 399 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash morbilliform			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin disorder			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Anuria			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder obstruction			

subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	1 / 399 (0.25%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	4 / 399 (1.00%)	4 / 199 (2.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage urinary tract			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst haemorrhage			

subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	4 / 399 (1.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure acute			
subjects affected / exposed	8 / 399 (2.01%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	1 / 8	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal tubular acidosis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 399 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 399 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urogenital disorder			
subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			

subjects affected / exposed	6 / 399 (1.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	7 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorder			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	12 / 399 (3.01%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	12 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	4 / 399 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary adrenocortical insufficiency			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary hypothyroidism			

subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	4 / 399 (1.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bone pain			
subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	2 / 399 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue mass			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 399 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			

subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 399 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	4 / 399 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis bacterial			

subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 399 (0.75%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 399 (0.75%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			

subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	13 / 399 (3.26%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 14	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 399 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 399 (0.50%)	6 / 199 (3.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection fungal			
subjects affected / exposed	0 / 399 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 399 (1.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	3 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	14 / 399 (3.51%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	9 / 16	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 399 (0.25%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			

subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 399 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	3 / 399 (0.75%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	3 / 399 (0.75%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 399 (0.25%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Ipilimumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	361 / 399 (90.48%)	166 / 199 (83.42%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	13 / 399 (3.26%)	10 / 199 (5.03%)	
occurrences (all)	13	10	
Hypertension			

subjects affected / exposed occurrences (all)	24 / 399 (6.02%) 27	7 / 199 (3.52%) 14	
Hypotension subjects affected / exposed occurrences (all)	21 / 399 (5.26%) 22	6 / 199 (3.02%) 7	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	61 / 399 (15.29%) 68	20 / 199 (10.05%) 23	
Fatigue subjects affected / exposed occurrences (all)	144 / 399 (36.09%) 169	55 / 199 (27.64%) 64	
Oedema peripheral subjects affected / exposed occurrences (all)	44 / 399 (11.03%) 45	9 / 199 (4.52%) 9	
Pain subjects affected / exposed occurrences (all)	25 / 399 (6.27%) 26	17 / 199 (8.54%) 14	
Pyrexia subjects affected / exposed occurrences (all)	63 / 399 (15.79%) 73	18 / 199 (9.05%) 21	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	45 / 399 (11.28%) 47	17 / 199 (8.54%) 19	
Dyspnoea subjects affected / exposed occurrences (all)	33 / 399 (8.27%) 36	9 / 199 (4.52%) 9	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	38 / 399 (9.52%) 39	9 / 199 (4.52%) 8	
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	31 / 399 (7.77%) 34	1 / 199 (0.50%) 1	

Aspartate aminotransferase increased			
subjects affected / exposed	27 / 399 (6.77%)	2 / 199 (1.01%)	
occurrences (all)	34	2	
Weight decreased			
subjects affected / exposed	61 / 399 (15.29%)	17 / 199 (8.54%)	
occurrences (all)	61	16	
Nervous system disorders			
Dizziness			
subjects affected / exposed	39 / 399 (9.77%)	17 / 199 (8.54%)	
occurrences (all)	43	19	
Dysgeusia			
subjects affected / exposed	21 / 399 (5.26%)	6 / 199 (3.02%)	
occurrences (all)	21	6	
Headache			
subjects affected / exposed	73 / 399 (18.30%)	24 / 199 (12.06%)	
occurrences (all)	84	24	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	31 / 399 (7.77%)	12 / 199 (6.03%)	
occurrences (all)	34	12	
Eye disorders			
Vision blurred			
subjects affected / exposed	21 / 399 (5.26%)	1 / 199 (0.50%)	
occurrences (all)	21	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	50 / 399 (12.53%)	13 / 199 (6.53%)	
occurrences (all)	61	14	
Constipation			
subjects affected / exposed	84 / 399 (21.05%)	37 / 199 (18.59%)	
occurrences (all)	96	42	
Diarrhoea			
subjects affected / exposed	190 / 399 (47.62%)	48 / 199 (24.12%)	
occurrences (all)	312	63	
Nausea			

subjects affected / exposed occurrences (all)	115 / 399 (28.82%) 144	36 / 199 (18.09%) 42	
Vomiting subjects affected / exposed occurrences (all)	75 / 399 (18.80%) 95	18 / 199 (9.05%) 19	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	123 / 399 (30.83%) 146	21 / 199 (10.55%) 24	
Rash subjects affected / exposed occurrences (all)	145 / 399 (36.34%) 195	22 / 199 (11.06%) 27	
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	13 / 399 (3.26%) 19	11 / 199 (5.53%) 12	
Pollakiuria subjects affected / exposed occurrences (all)	18 / 399 (4.51%) 18	10 / 199 (5.03%) 10	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	25 / 399 (6.27%) 26	0 / 199 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	51 / 399 (12.78%) 55	33 / 199 (16.58%) 33	
Back pain subjects affected / exposed occurrences (all)	69 / 399 (17.29%) 74	42 / 199 (21.11%) 43	
Bone pain subjects affected / exposed occurrences (all)	21 / 399 (5.26%) 24	14 / 199 (7.04%) 14	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	8 / 399 (2.01%) 10	10 / 199 (5.03%) 10	

Musculoskeletal pain subjects affected / exposed occurrences (all)	41 / 399 (10.28%) 47	27 / 199 (13.57%) 30	
Myalgia subjects affected / exposed occurrences (all)	24 / 399 (6.02%) 27	9 / 199 (4.52%) 11	
Neck pain subjects affected / exposed occurrences (all)	8 / 399 (2.01%) 9	11 / 199 (5.53%) 11	
Pain in extremity subjects affected / exposed occurrences (all)	45 / 399 (11.28%) 48	27 / 199 (13.57%) 30	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	31 / 399 (7.77%) 36	15 / 199 (7.54%) 18	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	114 / 399 (28.57%) 124	30 / 199 (15.08%) 35	
Dehydration subjects affected / exposed occurrences (all)	31 / 399 (7.77%) 34	6 / 199 (3.02%) 6	
Hypokalaemia subjects affected / exposed occurrences (all)	25 / 399 (6.27%) 30	5 / 199 (2.51%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2011	Added pre-dose thyroid-stimulating hormone (TSH) testing to the protocol in order to ensure consistency with the Food and Drug Administration (FDA) approved label for ipilimumab.
04 October 2012	Updated AE/SAE follow-up period from 70 to 90 days after the last dose of blinded study drug, and clarified on weight-based dose calculations to ensure consistency with other ipilimumab studies.
17 April 2014	Reordered the hierarchical order of testing for secondary endpoints, introduced radiologic Progression Free Survival (rPFS), time to pain increase, time to opioid analgesic use, and time to subsequent treatment (hormonal, non-hormonal, immunotherapy) as a pre-specified exploratory endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The further developments were not pursued as study did not meet its primary endpoint of demonstrating a statistically significant prolongation of overall survival.

Notes: